

Hospitalized pandemic influenza A (H1N1) patients in a university hospital

Research Article

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Abstract: The purpose of this study was to describe the demographic and clinical features of hospitalized patients with the pandemic H1N1 influenza A virus infection in a tertiary care hospital in Central Anatolia, Turkey. The patients, all over 16 years of age and hospitalized for influenza-like symptoms between 1 November 2009 and 31 December 2009, were retrospectively identified from the records of the Infectious Diseases Department. Eighty patients whose diagnoses were confirmed by real-time PCR were included in this study. The median age of the patients was 27 years; 41 of them were male. Thirty-seven of the patients had a radiologically proven pneumonia. Eighteen of 37 (48.6%) patients with pneumonia had an underlying co-morbid medical condition, and 14 required intensive care unit admission. Patients with pneumonia had higher levels of C-reactive protein. All patients but one received oseltamivir treatment. Six patients with pneumonia received only antiviral therapy, while 31 of the patients with pneumonia received concomitant antibiotic therapy. Three patients who required mechanical ventilatory support died due to respiratory insufficiency. Although our study implicates the later periods of the pandemic, there were no significant differences for patients' characteristics between our study and previous reports from the countries where the pandemic first occurred.

Keywords: Pandemic influenza • Swine origin influenza A H1N1 • Turkey

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1. Introduction

An influenza pandemic caused by a novel swine-origin influenza A H1N1 virus has been a worldwide concern since April 2009. The first cases of human infection with pandemic influenza A (H1N1) were observed in Mexico and the United States [1,2]. As of 31 January 2010, the World Health Organization (WHO) reported at least 15,174 deaths in laboratory-confirmed cases of pandemic influenza H1N1 2009 [3]. In the majority of patients, the disease has taken a mild clinical course. However, severe complications requiring hospitalization or intensive care treatment have occurred in isolated cases.

In Turkey, the first case of influenza A H1N1 was detected on 15 May 2009 and, as of 19 January 2010, death occurred in 627 laboratory-confirmed novel

influenza H1N1 patients despite the control measures [4,5]. The purpose of this study was to describe the demographic and clinical characteristics of the laboratory-confirmed pandemic influenza H1N1 2009 in patients hospitalized in a university hospital in Central Anatolia, Turkey.

2. Material and Methods

This study was performed at Erciyes University Hospital, a 1300-bed, tertiary care hospital, in Kayseri, Turkey. The hospital serves nearly 4 million people the city. Under normal conditions, the infectious diseases clinic has 19 single-bed rooms. After the number of the influenza cases began to increase, the medical management of the hospital decided to reserve the infectious diseases clinic for influenza cases only. Seven out of 19 rooms

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Table 1. Demographic features and symptoms of the patients on admission.

	Uncomplicated influenza (n=43) (%)	Influenza pneumonia (n=37) (%)	Total (n=80) (%)	P value
Age (median) (range), years	25 (17-62)	38 (17-62)	27 (17-62)	0.013
Male	22 (51.2)	19 (51.4)	41 (51.2)	NS
Admitted from home	40 (95.2)	36 (97.3)	76 (96.2)	NS
Contact with a patient with influenza-like symptoms	22 (51.2)	13 (35.1)	35 (43.7)	NS
Contact with a confirmed influenza (H1N1) case	1 (2.3)	0 (0.0)	1 (1.3)	NS
Symptoms				
Fever	38 (88.4)	33 (89.2)	71 (88.8)	NS
Headache	30 (69.8)	17 (45.9)	47 (58.8)	0.041
Myalgia	31 (72.1)	24 (64.9)	55 (68.8)	NS
Artralgia	33 (76.7)	23 (62.7)	56 (70.0)	NS
Sore throat	27 (62.8)	24 (64.9)	51 (63.8)	NS
Cough	39 (90.7)	33 (89.2)	72 (90.0)	NS
Sputum	20 (46.5)	13 (35.1)	33 (41.3)	NS
Chest pain	8 (18.6)	12 (32.4)	20 (25.0)	NS
Nausea	16 (37.2)	17 (45.9)	33 (41.3)	NS
Vomiting	11 (25.6)	12 (32.4)	23 (28.8)	NS
Diarrhea	4 (9.3)	6 (16.2)	10 (12.5)	NS
Days from first symptom onset to admission (median) (range)	3 (1-11)	3 (1-20)	3 (1-20)	NS

NS; not significant

were set up as an intensive care unit (ICU). Patients admitted to hospital because of symptoms compatible with influenza were managed according to WHO guidelines [6]. Oropharyngeal or nasopharyngeal swabs were obtained from patients and shipped to the influenza reference laboratory, Refik Saydam National Public Health Agency (RSHM), located in Ankara, the capital city of Turkey. Influenza A H1N1 was detected by the real-time PCR protocol provided by the United States Centers for Disease Control and Prevention [4].

The patients were all older than 16 years of age, hospitalized for an influenza-like syndrome between 1 November 2009 to 31 December 2009, and retrospectively identified from the records of the Infectious Diseases Department. Only laboratory-confirmed cases were included in this study. Uncomplicated influenza was defined as having one of the symptoms, including fever, cough, sore throat, headache, myalgia, arthralgia, and diarrhea or vomiting, but no shortness of breath and no dyspnoea, and a positive RT-PCR [6]. Influenza pneumonia was defined as an acute respiratory illness with positive RT-PCR and radiologic findings compatible with pneumonia [7,8].

The medical charts and discharge summaries of the patients were reviewed to identify demographic data, underlying medical conditions, clinical signs and symptoms, laboratory tests, chest radiographs, and treatment course. Treatment decisions for patients were not standardized. The type of antibiotic and antiviral

therapy, ICU admission criteria, and endotracheal intubation were decided by the attending physicians of the infectious diseases and intensive care medicine departments. Antiviral treatment was initiated without any delay for RT-PCR results.

The demographic and clinical features of the patients were analyzed using descriptive analyses. Categorical variables were described with the use of percentages, and medians were used for description of continuous variables. Patients with radiologically proven pneumonia were compared with others. We compared categorical variables using the chi-square or the Fisher exact test; continuous variables were compared using the Student *t* test or the Mann-Whitney U test, according to data distribution. Statistical analyses were performed with SPSS for Windows (revision 15.0, SPSS Inc., Chicago, IL, USA). A *p* value of <0.05 was considered significant.

3. Results

Between 01 November 2009 and 31 December 2009, 234 patients were hospitalized for influenza-like illness. Oropharyngeal or nasopharyngeal swabs were obtained from 115 patients; 80 swabs were reported as positive. Thirty-seven of the patients had radiologically proven pneumonia. The median age of the patients was 27 years; 41 were male. Forty-four patients were between

Table 2. Underlying medical conditions and treatment characteristics of the patients.

	Uncomplicated influenza(n=43) (%)	Influenza pneumonia(n=37) (%)	Total(n=80) (%)	P value
Underlying co-morbid condition				
Diabetes mellitus	3 (7.0)	1 (2.7)	4 (5.0)	NS
COPD	0 (0.0)	4 (10.8)	4 (5.0)	0.042
Asthma	3 (7.0)	2 (5.4)	5 (6.3)	NS
Congestive heart failure	2 (4.7)	0 (0.0)	2 (2.5)	NS
Coronary arterial disease	1 (2.3)	0 (0.0)	1 (1.3)	NS
Chronic renal failure	1 (2.3)	0 (0.0)	1 (1.3)	NS
Renal transplantation	4 (9.3)	0 (0.0)	4 (5.0)	NS
Liver transplantation	0 (0.0)	1 (2.7)	1 (1.3)	NS
Allo-SCT	2 (4.7)	1 (2.7)	3 (3.8)	NS
Hematologic malignancy	1 (2.3)	2 (5.4)	3 (3.8)	NS
Acute myeloid leukemia	1	1	2	
Acute lymphoblastic leukemia	0	1	1	
Solid tumour	0 (0.0)	2 (5.4)	2 (2.5)	NS
Breast cancer	0	1	1	
Lung cancer	0	1	1	
Romatoid arthritis	0 (0.0)	2 (5.4)	2 (2.5)	NS
Neurological disorder	2 (4.7)	1 (2.7)	3 (3.8)	NS
Epilepsy	2	0	2	
Myasthenia gravis	0	1	1	
Pregnancy	5 (11.6)	2 (5.4)	7 (8.8)	NS
Postpartum	0 (0.0)	1 (2.7)	1 (1.3)	NS
ICU support	1 (2.3)	14 (37.8)	15 (18.8)	<0.001
Mechanical ventilatory support	0 (0.0)	5 (13.5)	5 (6.3)	0.018
Non-invasive mechanical ventilatory support	0 (0.0)	5 (13.5)	5 (6.3)	0.018
Duration of hospitalization (median) (range) days	2 (1-13)	5 (3-30)	3 (1-30)	<0.001
Antibacterial administration	2 (4.6)	31 (83.7)	33 (41.3)	NA

NS; not significant, COPD; Chronic obstructive pulmonary disease, Allo-SCT; Allogenic stem cell transplantation, ICU; intensive care unit, NA; not assessed

17 and 30 years old and 23 of the patients were between 30 and 50 years old. Only two patients were older than 60 years. The median age of the patients with pneumonia was 37 years, and they were older than the patients with uncomplicated influenza ($p=0.013$).

Of the 80 patients, 76 were admitted from their home; three patients were admitted from a student hostel and one from a military garrison. The most common symptoms for patients on admission were cough and fever. Headache was more common in patients with uncomplicated influenza ($p=0.041$). Duration of symptoms before admission was similar for each group of patients. Thirty-five of the patients had a history of contact with a patient with influenza-like illness. The demographic features and symptoms of the patients on admission are shown in Table 1.

Eighteen out of 37 (48.6%) patients with pneumonia had an underlying co-morbid medical condition, while 24 (55.8%) of the 43 uncomplicated influenza cases

had an underlying co-morbid medical condition. Chronic obstructive pulmonary disease was more common in patients with pneumonia ($p=0.042$). Seven of the patients were pregnant and two of them had delivery after 37 weeks' gestation during hospitalization. We did not detect any adverse pregnancy outcomes such as preterm labor and spontaneous abortions.

Fourteen of the patients with pneumonia required ICU admission; 5 of them received endotracheal intubation and mechanical ventilation and 5 received non-invasive mechanical ventilatory support. Only one patient without pneumonia was admitted to ICU because of symptomatic bradycardia. His ECG showed sinus bradycardia. Echocardiography did not show any pathological changes. He was successfully discharged to the infectious diseases ward after three days of monitoring, and oseltamivir treatment was completed to 7 days. The median duration of ICU stay of pneumonia cases was 8 (range, 3–21) days. Ventilator-associated

Table 3. Physical examination findings and laboratory characteristics of the patients on admission.

	Uncomplicated influenza (n=43)	Influenza pneumonia (n=37)	Total (n=80)	P value
Physical examination findings				
Axillar fever (°C), (median) (range)	38.1 (36.0-39.8)	38.0 (36.0-39.5)	38.1 (36.0-39.8)	NS
Respiratory rate, bpm, (median) (range)	22 (18-32)	24 (20-36)	24 (18-36)	0.002
Body mass index > 35	2 (5.3)	7 (19.4)	9 (12.2)	NS
Laboratory findings				
Hemoglobin, g/dL, (median) (range)	13.8 (9.7-15.9)	12.7 (8.7-17.6)	13.4 (8.7-17.6)	NS
Total leukocyte count, (x10 ⁹ /L), (median) (range)	7.68 (2.81-15.37)	6.5 (0.81-36.15)	7.27 (0.81-36.15)	NS
Neutrophil %	72 (34-90)	75 (0.1-90)	74 (0.1-90)	NS
Platelet count (x10 ⁹ /L), (median) (range)	215 (102-366)	195 (1.16-564)	210.5 (1.16-564)	NS
CRP, mg/dL, (median) (range) ^a	15 (3-139)	51 (14-448)	40 (3-448)	0.001
ESR, (mm/h), (median) (range) ^b	37.5 (2-109)	46.5 (11-120)	43.5 (2-120)	NS
Creatinine, mg/dL, (median) (range)	1.1 (0.6-7.4)	0.9 (0.6-2.1)	1 (0.6-7.4)	NS
BUN, mg/dL, (median) (range)	11.8 (4.2-54)	12.4 (5.4-72)	12 (4.2-72)	NS
AST, U/L, (median) (range)	24 (8-76)	40 (13-552)	28.5 (8-552)	<0.001
ALT, U/L, (median) (range)	23 (11-78)	34 (7-553)	27.5 (7-553)	0.008
LDH, U/L, (median) (range) ^c	244 (23-596)	460 (201-1160)	306.5 (23-1160)	<0.001
CPK, U/L, (median) (range) ^d	91.5 (25-422)	206 (48-1405)	140 (25-1405)	0.001

NS; not significant, bpm; breaths per minute, CRP; C-reactive protein, ESR; erythrocyte sedimentation rate, BUN; blood urea nitrogen, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, CPK; creatinine phosphokinase

^a Data available for 50 patients

^b Data available for 40 patients

^c Data available for 72 patients

^d Data available for 59 patients

pneumonia developed in five of the mechanically ventilated patients. Three patients (3.8%) in the ICU died due to respiratory insufficiency. None of these patients suffered from any underlying illness.

All patients but one received oseltamivir treatment. The only patient who did not receive antiviral therapy was a 21-year old, otherwise healthy man hospitalized for dehydration and tonsillopharyngitis. He was discharged to home in good condition after a one-day hospitalization without any antiviral or antibacterial therapy. The median duration from the onset of the symptoms to oseltamivir initiation was three days and median duration of antiviral therapy was 5 days (range, 5–15 days). Six patients with pneumonia received only antiviral therapy, while 31 of the patients with pneumonia received concomitant antibiotic therapy. Antibiotics were administered in two of the uncomplicated influenza cases. One of these patients received moxifloxacin for sinusitis, and a pregnant women received ceftriaxone for a urinary tract infection. Respiratory quinolones, either levofloxacin in 20 patients or moxifloxacin in 6 patients, were the preferred antibiotics in patients with pneumonia. Seven of the patients admitted to the ICU with pneumonia received an oseltamivir dose of 300 mg/day. Median duration of hospitalization was 2 days for uncomplicated influenza cases and 5 days for patients with pneumonia ($p < 0.001$). The underlying medical

conditions and treatment characteristics of the patients are shown in Table 2.

Radiological evaluations were available for 78 patients. Two of the pregnant patients without any respiratory stress refused to have a chest X-ray. Twenty-eight of the patients had bilateral, predominantly basal, patchy alveolar opacities, while 11 patients had unilateral consolidations.

The physical examination findings and laboratory results of the patients on admission are shown in Table 3. Tachypnea was statistically prevalent in patients with pneumonia, as expected ($p = 0.002$). The leukocyte count was under 4000/mm³ in 16 patients and above 11000/mm³ in 12. Thrombocytopenia ($< 150,000/\text{mm}^3$) was observed in 14 patients. Alanine aminotransferase (ALT) was higher than 40 U/L in 17 patients and aspartate aminotransferase (AST) was higher than 40 U/L in 25 patients. Lactate dehydrogenase (LDH) was higher than 245 U/L in 48 patients, and creatinine phosphokinase (CPK) was higher than 145 U/L in 27. Patients with pneumonia had higher levels of C-reactive protein (CRP), ALT, AST, LDH, and CPK, while hemoglobin levels, total leukocyte count, and neutrophil percentages were similar (Table 3). Sixteen patients presented with creatinine levels higher than 1.2 mg/dL. One of them had chronic renal failure and all other patients improved without hemodialysis.

Serum procalcitonine level was measured in 23 patients on admission. In 8 patients with uncomplicated influenza procalcitonine, levels were under 0.05 ng/mL. Four patients with pneumonia had a procalcitonin <0.05 while the level was between 0.08 and 5.6 ng/mL for 11 patients.

Blood cultures were performed with 66 patients and sputum cultures were done on 16 on admission. There was no clinically significant growth from blood and sputum cultures except for a patient with pneumonia whose sputum culture was positive for *Streptococcus pneumoniae*.

4. Discussion

In this study we report the demographic and clinical characteristics of 80 hospitalized patients with laboratory-confirmed pandemic influenza H1N1 virus infection. Although this novel influenza strain is highly transmittable from person to person, severe human disease occurs at low frequency. Severe pneumonia has been reported in previously healthy young adults [6]. In our cohort, the median age was 38 years for patients with pneumonia. The median age of the patients admitted to the ICU because of severe respiratory failure caused by influenza H1N1 was 36 years in Spain and 29 years in the U.S. [7,9].

Pregnancy and obesity were also reported as important risk factors for severe influenza [7-11]. The body mass index was higher than 35 in 7 out of 37 patients with pneumonia in our cohort (Table 3). A postpartum patient experienced severe pneumonia; she recovered successfully after long-term mechanical ventilatory support. Even before the emergence of the novel 2009 H1N1 strain, influenza disease was a serious complication in patients with underlying medical conditions. An analysis of 272 patients of 2009 pandemic H1N1 influenza A in the U.S. showed nearly three-quarters of the patients had one or more underlying medical condition [9]. In a study from Spain, 17 of 32 critical pandemic influenza patients had an underlying co-morbidity [7]. Of the 78 confirmed pandemic influenza cases diagnosed in UK, 54 had underlying medical problems [12]. Compared to these study groups, our patients had a similar rate of chronic diseases and underlying medical conditions, such as pregnancy and obesity.

Bacterial co-infection has been considered an important problem for patients with influenza. The prevalence of concurrent bacterial pneumonia with *S. pneumoniae*, *Staphylococcus aureus*, or *Streptococcus pyogenes* was 29% in 77 fatal cases of pandemic

influenza A H1N1 virus infection [13]. In our study, we detected *S. pneumoniae* co-infection in only one patient. The 6 out of 37 patients with pneumonia were completely cured without any antibiotics. We believe that patients with mild pneumonia could be treated without antibiotics under close follow-up. However, ruling out bacterial co-infection is difficult in patients with pneumonia. CRP and procalcitonine levels are increased during the acute lung injury stage of pneumonia and, in our study, patients with pneumonia had higher CRP levels when compared to uncomplicated influenza cases (Table 3). A recent study showed that low procalcitonine values, combined with low CRP levels, suggest primary influenza. The study indicated that none of the 16 patients with pandemic influenza H1N1 infection had a CRP level higher than 140 mg/L and procalcitonine higher than 5.9 ng/mL [14]. In our analysis, 1 out of 37 patients with pneumonia had a CRP level higher than 130 mg/dL; this was the patient who had *S. pneumoniae* co-infection.

Elevated LDH and CK at hospital admission have been suggested as prognostic indicators of severe disease [7]. We observed statistically significant higher levels of LDH, CK, AST, and ALT in patients with pneumonia when compared with uncomplicated influenza.

The mortality due to pandemic influenza is 7% in U.S. and 2.3% in Argentina [9,15]. Among the 80 patients we analyzed, mortality was 3.8%. However, 20% of the patients (3 out of 15) requiring intensive care support died. This was similar to the reports from Spain and UK [5-10].

The epidemiological and clinical characteristics of pandemic influenza A H1N1 virus infection has been described clearly in the early reports from the countries attacked in the first months of the pandemic [7,9,10,12,15-17]. Although our study implicates the later periods of the pandemic, there were no significant differences for patients' characteristics between our report and recent studies from the U.S., Spain, UK, Mexico, and Argentina. We believe that sharing the experience regarding management of influenza H1N1 2009 cases at different periods of pandemics will allow the scientific community to develop better strategies to struggle against the 21st century's first pandemic.

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